(Rel.82A—12/99 Pub.605) FORM 13-18 13-159

Practitioner's Docket No. 1581/128WO

CHAPTER II

Preliminary Classification:

Proposed Class:

Subclass:

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.'" M.P.E.P., § 601, 7th ed.

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GR99/00030	13 August 1999 (13/08/99)	14 August 1998 (14/08/98)

TITLE OF INVENTION Use or Misoprostol and/or Metabolites of Misoprostol for Treating Sexual Dysfunction in Women (as amended)

APPLICANT(S)
Karouzakis, Petros et al.

Box PCT
Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date 09 February 2001, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL 725604562 US, addressed to the: Commissioner for Patents, Washington, D.C. 20231.

Harriet M. Strimpel, D. Phil.
(type or print name of person mailing paper)

Harriet Strimpel
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO, and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing—See 37 C.F.R. § 1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 U.S.C. § 371 otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).

I. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. § 371:

a. ☐ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
☐*	TOTAL CLAIMS	21 −20=	1	× $18.00=	$ 18.00
	INDEPENDENT CLAIMS	3 −3=	0	× $78.00=	0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	
BASIC FEE**	☐ U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: ☐ and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(1) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. § 1.492(a)(4)) ..... $96.00 ☐ and the above requirements are not met (37 C.F.R. § 1.492(a)(1)) ..... $670.00 ☒ U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: ☐ has been paid (37 C.F.R. § 1.492(a)(2)) ..... $690.00 ☐ has not been paid (37 C.F.R. § 1.492(a)(3)) ..... $970.00 ☒ where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. § 1.492(a)(5)) $840.00				860.00
	Total of above Calculations				= 878.00
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (note 37 C.F.R. § 1.9, 1.27, 1.28)				−
	Subtotal				
	Total National Fee				$
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. § 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL	Total Fees enclosed				$

*See attached Preliminary Amendment Reducing the Number of Claims.

i. ☒ A check in the amount of $878.00 to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of _____
A duplicate copy of this sheet is enclosed.

**WARNING: *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. ☒ A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. ☐ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☒ has been transmitted

i. ☒ by the International Bureau.
Date of mailing of the application (from form PCT/1B/308): 24 February 2000

ii. ☐ by applicant on _____.
Date

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☐ is transmitted herewith.

b. ☒ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____.
Date

d. ☐ will follow.

5. ☐ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: *The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.*

a. ☐ are transmitted herewith.

b. ☐ have been transmitted

i. ☐ by the International Bureau.
Date of mailing of the amendment (from form PCT/1B/308): _____.

ii. ☐ by applicant on (date) _____.
Date

c. ☒ have not been transmitted as

i. ☒ applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210.): 03/12/99

ii. ☐ the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the amendments were made in the English language.

c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ A copy of the international examination report (PCT/IPEA/409)

☒ is transmitted herewith.

☐ is not required as the application was filed with the United States Receiving Office.

8. ☐ Annex(es) to the international preliminary examination report

a. ☐ is/are transmitted herewith.

b. ☐ is/are not required as the application was filed with the United States Receiving Office.

9. ☐ A translation of the annexes to the international preliminary examination report

a. ☐ is transmitted herewith.

b. ☐ is not required as the annexes are in the English language.

10. ☒ An oath or declaration of the inventor (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. ☐ was previously submitted by applicant on _____ JC05 Rec'd PCT/PTO 09 FEB 2001
Date

b. ☐ is submitted herewith, and such oath or declaration

i. ☐ is attached to the application.

ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. § 1.70.

c. ☒ will follow.

II. Other document(s) or information included:

11. ☐ An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

a. ☐ is transmitted herewith.

b. ☐ has been transmitted by the International Bureau.
Date of mailing (from form PCT/IB/308): _____.

c. ☐ is not required, as the application was searched by the United States International Searching Authority.

d. ☒ will be transmitted promptly upon request.

e. ☐ has been submitted by applicant on _____.
Date

12. ☒ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:

a. ☐ is transmitted herewith.

Also transmitted herewith is/are:

☐ Form PTO-1449 (PTO/SB/08A and 08B).

☐ Copies of citations listed.

b. ☒ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).

c. ☐ was previously submitted by applicant on _____.
Date

13. ☐ An assignment document is transmitted herewith for recording.

A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

_____

_____

_____

14. ☒ Additional documents:

a. ☐ Copy of request (PCT/RO/101)

b. ☒ International Publication No. WO00/09134

i. ☒ Specification, claims and drawing

ii. ☐ Front page only

c. ☒ Preliminary amendment (37 C.F.R. § 1.121)

d. ☐ Other

_____

_____

_____

15. ☒ The above checked items are being transmitted

a. ☒ before 30 months from any claimed priority date.

b. ☐ after 30 months.

16. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____, namely:

_____

_____

_____

_____

_____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 19-4972

☐ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

☐ 37 C.F.R. § 1.492(b), (c) and (d) (presentation of extra claims).

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

☐ 37 C.F.R. § 1.17 (application processing fees)

☐ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☐ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

Reg. No.: 37,008

Tel. No.: (617)443-9292

Customer No.: 002101

Harriet Strimpel

SIGNATURE OF PRACTITIONER

Harriet M. Strimpel, D. Phil.

(type or print name of practitioner)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Karouzakis et al.	Docket No. 1581/128
Serial No.:	Not yet assigned	Art Unit: Not yet assigned
Date Filed:	filed herewith	Examiner: Not yet assigned
Invention:	USE OF MISOPROSTOL AND/OR METABOLITES OF MISOPROSTOL FOR TREATING SEXUAL DYSFUNCTION IN WOMEN (as amended)	Date: 09 February 2001

Commissioner for Patents
BOX PCT
Washington, DC 20231
Attn: EO/US

EXPRESS MAIL CERTIFICATE

Express Mail No: EL 725604562 US
Date of Mailing: 09 February 2001

I hereby certify that the attached papers listed below are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the Commissioner for Patents, Box PCT, Washington, DC 20231, Attention: EO/US.

Harriet M. Strimpel, D.Phil.

Preliminary Amendment

Dear Sir:

Please amend the application as follows:

In the claims:

Please cancel claims 1-5 and add new claims 6-27.

6. A method for treating sexual dysfunction in a female subject, comprising
   (a) selecting a formulation containing at least one of misoprostol and a metabolite of misoprostol in an effective dose; and
   (b) topically administering the formulation to the subject to provide a beneficial treatment for sexual dysfunction.

7. A method according to claim 6, wherein the formulation is applied to the vagina or the clitoris.

8. A method according to claim 7, wherein the misoprostol or a metabolite of misoprostol is selected from the group consisting of a racemic mixture, an enantiomer in a (+) or (-)R form and an enantiomer in a (+) or (-)S form.

9. A method according to claim 6, wherein the formulation includes a galenic preparation.

10. A method according to claim 6, wherein the formulation is selected from the group consisting of a gel, an aqueous solution, an ointment, vaginal ovules and a system of controlled transdermal absorption.

11. A method according to claim 6, further comprising a vasodilatory agent additional to the at least one of misoprostol and its metabolite for providing an enhanced beneficial treatment of sexual dysfunction in the subject.

12. A method according to claim 11, wherein the additional vasodilatory drug is alprostadil.

13. A method according to claim 6, further comprising a passage accelerator for increasing absorption of at least one of misoprostol and a metabolite of misoprostol and optionally an additional vasodilator.

14. A method according to claim 6, further comprising an agent for treating sexual dysfunction that minimizes adverse effects arising from an otherwise toxic amount of the misoprostol or the metabolite of misoprostol and enhances the beneficial treatment of sexual dysfunction.

15. A method according to claim 14, wherein the agent is a-cyclodextrin.

16. A method according to claim 15, wherein the beneficial effect is vasodilation leading to sexual desire.

17. A method according to claim 6, wherein the formulation comprises a gel.

18. A method according to claim 17, wherein the gel is a low viscosity gel.

19. A method according to claim 6, wherein the formulation comprises a vanishing cream formulation.

20. A method according to claim 6, wherein the formulation comprises gelatin.

21. A method for treating sexual dysfunction in a female subject, comprising

(a) providing a mixture including misoprostol or misoprostol metabolite, hydroxypropyl methylcellulose and water; and

(b) administering the mixture to a female subject.

22. A method according to claim 21, wherein the effective dose of misoprostol or misoprostol metabolite is in the range of 0.3-0.9% w/v, and the formulation further includes hydroxypropyl methyl cellulose comprising hydroxypropyl methyl cellulose 3000 at about 4% w/v.

23. A pharmaceutical composition, comprising an effective dose of at least one of misoprostol or misoprostol metabolite for treating sexual dysfunction in women.

24. A pharmaceutical composition according to claim 23, further comprising a methylcellulose.

25. A pharmaceutical composition according to claim 24, wherein the methylcellulose is selected from carboxymethylcellulose and hydroxypropyl methyl cellulose.

26. A pharmaceutical composition according to claim 18, further comprising a mixture of more than one vasodilatory agent.

In the specification

Please delete the title "Use of Misoporstol or/and Misoprostol acid for Preparing Drug in order to cure Sexual Dysfunction in Women." and add --Use of Misoprostol and/or Metabolites of Misoprostol for Treating Sexual Dysfunction in Women--

Conclusion

In view of the foregoing amendments, applicant submits that the claims are now in condition for allowance. Early and favorable reconsideration of the application is therefore respectfully solicited.

It is believed that no extension of time is required, however, in the event that an extension is required, applicants hereby petition same and request that any extension or other fee required for the timely consideration of this application be charged to Deposit Account No. 19-4972.

Respectfully submitted,

Harriet M. Strimpel, D.Phil
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Attorney for Applicants
Bromberg & Sunstein, LLP
125 Summer Street
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(617) 443-9292

Date: February 9, 2001
144573

USE OF MISOPROSTOL OR/AND MISOPROSTOL ACID FOR PREPARING DRUG IN ORDER TO CURE SEXUAL DYSFUNCTION IN WOMEN.

The invention relates to the use of an already known pharmaceutical substance, misoprostol as well as its first metabolite, misoprostol acid, for preparation of a drug for external use which is destined to cure sexual dysfunction in women.

The problem of the female sexual dysfunction even though it has been setted by the modern medicine decades ago, it hasn't been yet confronted with efficiency.
The extension of the problem is not quite known (Scrip Reports, March 1998), but according to an older research (Frank et al.,1978) the percentage of women facing a kind of dysfunction is going up to 63 %.

In our days the sexual dysfunction of women is being confronted either with surgical restoratoin, when -rarely- it has to do with anatomic problems, or with psychotherapy, that could be effective in cases where the causes are not functional, or even with the spesific treatment of substitution in cases where sexual inability has to do with hormonal disturbance.

These methods are being confronted with skeptikism, or because they are applying to a very small percentage of women (e.g.women with anatomic problems), either because they are characterized by a low efficiency, in accordance -many times- to an adverse relation between benefit and risk.

The interest of many searchers nowdays has been turned to the use of vasoactive substances, in accordance with the methods used in the treatment of male impotence. But these methods even though they are successfully used in men (for example intracavernosal injections), they strike against the female genital system

(inability of selfinjection into the corpora cavernosa of the clitoris), either the inefficiency of the methods that are for external use.

The present method aims at the removal of the disadvantages of the above methods with the use of a simple method, that consists of the local application of a vasoactive substance, known as misoprostol, to the clitoris or/and to the vagina, in order to cure sexual dysfunction in women due to vascular, hormonal, phychogenic or other cause.

Misoprostol is the general name of a synthetic prostaglandin belonging to the E_1 series (PGE_1 analogs). Synthesis:P.W.Collins,R.Pappo,Belgian patent 827.127, American patent 3.965.143 (The Merck Index,ed.Merck & Co. Inc,11th edition,1989,p.6128). Its chemical name is (11a,13E)-(±)-11,16-Dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester or (±)-(methyl)-(1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate or (±)-15-deoxy-(16RS)-16-hydroxy-16-methyl-PGE_1 methyl ester.It is consisted of 4 stereoisomers in about equal proportions [(+)&(-) enantiomers of 16R- and 16S-forms].(The Merck Index, 11th edition,1989,p.6128).The empirical formula is $C_{22}H_{38}O_5$.

Its structural formula appears in page 8, Fig.1.

Compared with other prostaglandins of group E_1 and especially alprostadil,misoprostol bears a methyl group (-CH_3) on the carbon atom of position 16.

According to a method which relates the biological action of various medicament molecules to its chemical structure it appears that due to this group we have a big penetration of misoprostol in the underlying tissues and a local vasodilation which cure sexual dysfunctions. Misoprostol is used today orally as antiulcer drug

(Physicians Desc Reference,PDR,ed.Medical Economics Data,Production Company at Montrale 48th edition,1994,P.2197-2199).

In particular it is administered for the prevention of gastric ulcer to patients who take non-steroid antiinflammatory drugs.It is available in the countries of Europe and U.S.A. by Searle Company under the commercial name Cytotec®.In none country is the drug mentioned as suitable for male impotence nor are there any relevant reports on the international bibliography.On a contrary amongst the undesirable effects in oral therapy with misoprostol is male impotence (Physicians Desc Reference, ed.Medical Economics Data,Production Company at Montrale,48th edition, 1994,p.2197-2199).

Misoprostol -compared to other vasodilatory drugs (e.g.nitroglycerin, Prostaglandin E_1 etc.)- cause a strong local vasodilation and as a result increase of the blood flow when it is used externally to the clitoris or/and to the vagina.Because of the local vasodilation is caused tumescence of the clitoris, intence bleeding of the vagina and feeling of sexual desire.Simultaneously, in women with anorgasmia of various causes, promote after masturbation or sexual intercourse, the coming of orgasm.

Equally strong topical vasodilation after external application is exerted by the hydrolysis product of misoprostol (misoprostol acid) which anyway constitutes the first misoprostol metabolite after its introduction in the organism (see page 8, Fig.2).

Last because of the intense topical vasodilatory action of misoprostol and the corresponding free acid,the two pharmaceutical molecules reinforce the absorption of other vasoactive substances (e.g.alprostadil) resulting in the occurrence of synergic action.

Misoprostol can be dissolved in water and its compatibility with excipients provides the opportunity of production of a variety of simple pharmacotechnical forms for external use, which are at the same time very well tolerated by the skin and the mucosa.

From the above mentioned description it appears that the most serious advantage of the method is the manner of administration of the drug (external in combination with the lack of undesirable action in the suggested doses or/and the proposed pharmacotechnical forms) the relatively low cost and especially the most satisfactory result together with corresponding methods.

Amongst the probable methods of application,most advantageous is a synthesis in the gel form of relatively low viscosity which contains

0,3-0,9 % w/v misoprostol in the methylform of methylester and/or free acid,a complexforming means,as 1,6% w/v a-cyclodextrine and substances suitable for the formation of a gel e.g.hydroxypropyl methylcellulose "3000" 2% w/v,propylene glycol 10% v/v and Water to 100 ml. The gel contains 3-9 mg of active substance per ml.

Method of application:0.1(or more,depending on responce) are applied to the clitoris or/and to the vagina.

9 examples related to the pharmacotechnical forms and the ways of application of misorostol:

1)0.10 ml gel,relatively low viscosity containing 0,3-0,9% w/v misoprostol for applying to the clitoris or/and to the vagina.

Synthesis:

1-1.Misoprostol	0,3-0,9 g
Hydroxypropyl Methylcellulose "3000"	2 g
Water purified to	100 ml
1-2.Misoprostol	0,3-0,9 g
Sodium Carboxymethylcellulose	2 g
Propylene Glycol	25 ml
Water purified to	100 ml

2)0,10 ml gel of relatively high viscosity,containing 0,30-0,90% w/v in misoprostol for vaginal application.

Synthesis:

2-1.Misoprostol	0,30-0,90 g
Hydroxypropyl Methylcellulose "3000"	4 g
Water purified to	100 ml
2-2.Misoprostol	0,30-0,90 g
Sodium Carboxymethylcellulose	4 g
Propylene Glycol	25 ml
Water purified to	100 ml

3)0,10 ml of aqueous solution of misoprostol containing 0,3-0,9% w/v for clitoral or/and vaginal application.The solution can also contain propylene glycol or glycerol in the corresponding proportions (e.g.10%) to increase the viscosity of the solution.

4)0,10 ml of ointment or emulsion o/w containing 0,3-0,9% w/w in misoprostol for clitoral or/and vaginal application,where misoprostol is found spread in the continuous (aqueous) phase.

Synthesis:

4-1.Misoprostol	0,3-0,9 g
Vanishing Cream to	100 g

(Although for the requirements of this example as Vanishing Cream we used Bepanthène® Cream of Roche,we have various creams o/w which are available in commerce or are described in National Pharmacopoeies and can be used for the same purpose).

5)Vaginal ovules of suitable dimensions,weight about 300-900 mg, containing 0,04-0,20% w/w misoprostol for vaginal use.

Synthesis:

5-1.Misoprostol	0,3-0,9 g
Glycerol	70 g
Gelatine	20 g
Water purified to	100 g

6)0,10 ml gel (or more depending of response) according to the examples (1-1) and (2-1) which contains moreover 1,6% w/v a-cyclodextrine.

7)0,10 ml gel (or more depending of response) according to the example (6) which contains moreover 10 ml ethyl alcohol 96° and 0,5 mg/ml alprostadil.

Notes:1)The incorporation of misoprostol in bases already mentioned took place in normal temperature (20-25°C) and at a temperature not exceeding 40°C.

2)No significant changes in misoprostol activity was observed as a function of pH,we observent however an important reduction or/and neutralization of misoprostol action in the presence of Polysorbate "80".

3)The time of appearance of the result varies from 20-40 minutes.The timing of the appearance and the intensity of the result seems to be able been positively influenced by certain moisturising agents (e.g.Propylene Glycol,Glycerol) as well as by certain substances which reinforce by various mechanisms the transcutaneous absorption (e.g.Urea,Acid Citric).

4)High once only doses of misoprostol (>1000) mcg to the clitoris or to the vagina) cause certain systematic undesirable effects as shudder,feeling of hard ship,excitement and diarrhea.The presence of a-cycodextrine reduces the undesirable effects and allows the application once only of higher doses without notable effect on the timing of its action but with positive effect on the intensity result and with prolonging of its duration.

5)The doses which are mentioned in the examples are only indicative since the intensity of the result depends,apart from the nature and the grade of the sexual dysfunction on other factors as e.g.the degree of moisturising of the underlying tissue,the physiological situation of the skin or the mucosa etc.As had already been mentioned, misoprostol is an extremely hydrophile molecule compared with other prostaglandins of E_1 series (e.g. with alprostadil which can be dissolved in alcohol but her solubility in water is only 8000 mcg/100 ml at 35°C).

This consists an important advantage:

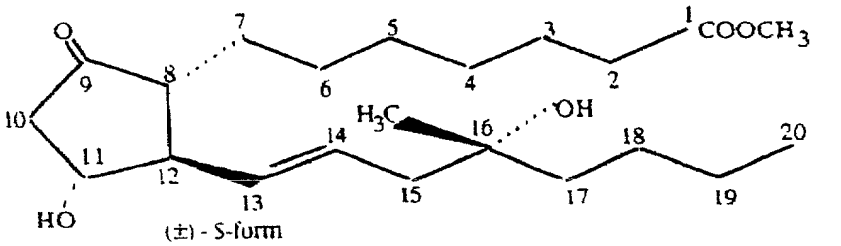
a)Because no use of organic factors is required (e.g.ethyl alcohol) which usually irritate tissues and are thus unsuitable for application on the skin and especially the mucus.

b)Because it allows the incorporation of active substances on a very small amount of excipient, suitable for application on surfaces of limited extent,as e.g.the clitoris.

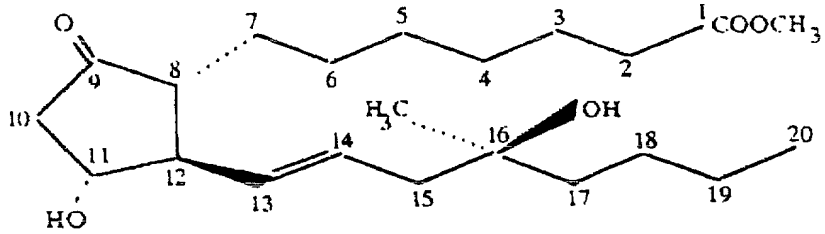
6)Misoprostol hasn't been accused for carcinogenic or teratogenic effect but because of the described irritation of the smooth uterine fibbers (Physicians Desc Reference,PDR,ed.Medical Economics Data,Production Company at Montrale 48th edition.1994,P.2197-2199), misoprostol must not becoming in touch with the genital system of the women who are pregnant.

STRUCTURAL FORMS

Fig. 1.Misoprostol

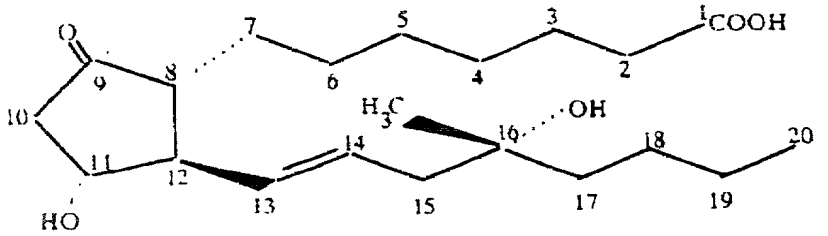


(±) - S-form

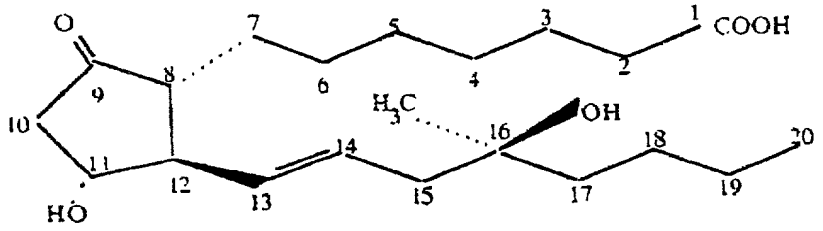


(±) - R- form

Fig. 2.Misoprostol acid



(±) - S- form



(±) - R - form

Claims

1)The use of misoprostol or/and its first metabolite, misoprostol acid,for the production of a drug applied topically to the clitoris or/and to the vagina and is destined for the therapy of sexual dysfunction in women due to vascular or other causes.

2)The use of misoprostol and/or its metabolite (misoprostol acid) according to claim (1) either as racemic mixtures or in the form of one of the stereoisomers from which they consist:[(±)-R form & (±)-S form].

3)The use of misoprostol and misoprostol acid according to claims (1) and (2) in the form of various galenic preparations (solutions,ointments,endourethral sticks,systems of controlled transdermal absorption) which,according to the general principles of pharmacotechnics, facilitate the application and precise administration of the right doses for the achievement of the desired therapeutical or diagnostic aim as described in claim (1).

4)The use of misoprostol and misoprostol acid according to claim (1),(2) and (3) in combination with other vasodilatory drugs as alprostadil for the appearance of synergistic action, as well as "passage accelerators" used normally in pharmaceutical technology aiming to increase absorption of drugs through the skin or the mucosa.

5)Use of misoprostol and misoprostol acid according to claim (1),(2) and (3) in combination with a-cyclodextrin or other substances which,according to the general methods used in pharmacotechny impedes or retards the appearance or undesired effects of the drug or prolong their pharmaceutical action.

Docket No.
1581/128

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Use of Misoprostol and/or Metabolites of Misoprostol for Treating Sexual Dysfunction in Women

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **February 9, 2001** as United States Application No. or PCT International Application Number **09/762,602**

and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
970100172	**Greece**	**14/08/98**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
PCT/GR98/00012	**PCT**	**13/08/99**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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